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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/005,196	ALLEN ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,8,9 and 35-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,8,9 and 35-47* is/are rejected.

7)☒ Claim(s) *6 and 9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/08/2004 has been entered.

Claims 1-5 have been cancelled. Claims 6,9,35-39 have been amended. Claims 40-47 have been added. Claims 6,8,9 and 35-47 are pending and under consideration in the instant office action.

Claim Objections

Claim 6 is objected to because of the following informalities: The gene name FPR-RS4 should be spelled in the first use of the abbreviation (line 12). Appropriate correction is required.

Claim 9 is objected to because of the following informalities: The claim requires a pseudopregnant mouse to give birth. However, by definition, a pseudopregnant mouse is not pregnant and cannot give birth. Furthermore, based on the method steps of the claim, the mouse that gives birth is pregnant, not pseudopregnant. Appropriate correction is required.

Claim Rejections - 35 USC § 101/112

Definitions:
[from REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS; repeated from http://www.uspto.gov/web/menu/utility.pdf]

> "Specific Utility" - A utility that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

"Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material, which has a stated correlation to a predisposition to the onset of a particular disease condition, would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)

C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility".

D. A method of making a material that itself has no specific, substantial, and credible utility.

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

See also the MPEP § 2107 - 2107.02.

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6,8,9 and 35-47 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility. The rejection set forth on pages 2-4 of the Final office action mailed 05/11/2004 is maintained and applied to newly added claims 40-47 for reasons of record.

The instant specification has discussed that the mice of the instant invention can be used as models of disease to screen for drug therapies and as a tool for studying the function of the

FPR-RS4 gene. As set forth in the previous office action, these uses fail to meet the standards of a well-established utility required under 35 U.S.C. 101.

Applicant has argued that the Patent Office guidelines state that a rejection for lack of utility may not be imposed where an invention has a well-established utility or is useful for any particular practical purpose (page 4, paragraph 4). Applicant does not understand how the invention cannot have utility when the invention is being used by one of skill in the art.

In response, the instant invention has failed to meet the requirements of possessing a well-established utility and for a use with any particular practical purpose. A well-established utility and a utility with a particular practical purpose is one that is specific and substantial (see MPEP 2107(II)(A)(3)(ii) and MPEP 2107 (II)(B)(1)). The utility of the instant invention is neither specific nor substantial for reasons of record (see pages 2-4 of the previous office action). Applicant is reminded that the utility guidelines (see above) expressly state that utilities requiring further research to identify or reasonable confirm a use do not define substantial utilities. Examples of uses that are not considered substantial utilities include basic research in studying the claimed product and use to screen for therapeutics for an unspecified disease. The use of the invention by the skilled artisan does not impart patentability or patentable use on the invention for reasons set forth above.

Applicant has argued that the utility of the mouse is credible (page 5, paragraph 2),

In response, for an invention to have patentable utility, the utility must meet all of the criteria of specific, substantial and credible. Meeting the requirement of having credible utility does not overcome the rejection on the grounds that the invention lacks specific and substantial utility.

Applicant has argued that there is utility for the claimed mice in studying gene function and that this use is well recognized in the art (page 5, paragraph 3).

In response, as set forth above, use of the mouse for studying gene function is not a substantial utility.

Applicant has referred to previous arguments of the amendment filed August 31, 2004 with respect to the principles set forth in *In re Brana*.

In response, no such reference to *In re Brana* is found in the amendment filed August 31, 2004. However, in a general respect, the fact pattern in Brana does not correlate to the fact pattern of the instant application. In Brana, the court addressed two separate issues, utility and enablement. The court held that the specification did, in fact, disclose a specific and substantial use for the compound, treating leukemia, and that this use was overlooked by the PTO in making the rejection under 101. The court observed that the claimed compound was similar in structure to compounds in the prior art that were useful in treating leukemia. The claimed compound behaved in a manner similar to that of the prior art in art accepted assays for anti-leukemic activity. Therefore, the specification enabled the use. The instant specification and the art of record fail to support such a patentable utility for the instant invention and therefore, the principles set forth in *In re Brana* do not apply to the instant invention.

Claim 8 is directed to cells having derived from the claimed mouse. The claimed cells lack specific and substantial for the reasons above and because the specification does not teach how to use the cells in any manner other than to make the mouse or when they are part of a mouse that is a model of disease.

In light of the above, the skilled artisan would not find the asserted utility of the transgenic mouse and cells encompassed by the claims to be specific and substantial.

Claims 6,8,9 and 35-47 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The following issues of enablement must also be addressed:

The previous rejections set forth on page 4 of the previous office action with respect to scope of enablement have been overcome by the instant claim amendments. However, the claims have been amended such that there are several new grounds of rejection, some of which were posed and overcome in earlier prosecution and are necessitated again by these further claim modifications.

1) The specification fails to enable making and using a mouse with a homozygous or heterozygous null FPR-RS4 allele wherein the mouse exhibits any phenotype, including wild type (claims 6,9,40,41,43-47). The specification also fails to enable making any heterozygous mice exhibiting any of the phenotypes listed in claims 35-39 and 42.

The breadth of the claims varies with respect to the phenotypes of the homozygous and heterozygous mice. Claims 6,9,40 and 41 fail to recite a phenotype and encompass mice exhibiting any phenotype, including wild type. Claims 35-39 and 42 encompass heterozygous mice exhibiting a specific phenotype that is not supported by the specification as the specification fails to teach that the heterozygous mice displayed any phenotype that differs from wild type.

The specification has taught that mice homozygous for a disruption of the FPR-RS4 gene set forth by SEQ ID NO:1 exhibit decreased time spent in a central region during an open field test (page 56, lines 6-11), decreased time to fall during a rotorod test, decrease in time to fall off the accelerating rotorod (page 57, lines 3-9) and increased dose of metrazol to reach seizure the second stage of seizure (page 57, lines 23-27). The specification has not taught any phenotype other than wild type for the heterozygotes as encompassed by the claims. The specification has not definitively linked the described behavioral phenotypes to any of the claimed disorders including increased anxiety.

The art at the time of filing held that the phenotype of transgenic knockout mice was unpredictable. Leonard (1995, Immunological Reviews, Vol. 148, pages 98-113) disclosed mice with a disruption in the g_c gene that was intended to be a model for X-linked severe combined immunodeficiency (XSCID), but display a variety of unexpected traits (abstract). These knockout mice were expected to have thymocytes with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (page 105, line 7). Griffiths (1998, Microscopy Research and Technique, Vol. 41, pages 344-358) taught that, despite a known role for the PLP gene based on spontaneous mutations in the gene, the knockout mouse failed to display any of the expected phenotypes (page 350, last paragraph). The art also held that there are problems inherent in using knockout animals as models of anxiety as it is known that modulation of anxiety and other emotional disorders involve multiple loci and that this phenotype can be greatly influenced by genetic background (refer to Belzung, 2001). As set forth on page 5 of the office action mailed, 09/10/2003, the specification and art of record fail to provide evidence correlating the observed phenotype for the claimed mice to increased anxiety.

Because the phenotype of a knockout mouse is unpredictable, one cannot predict or guess that the mice encompassed by the claims would exhibit any one of the infinite phenotypes broadly encompassed by the claims that do not recite a specific phenotype. The skilled artisan would not know how to make a mouse exhibiting any one of the phenotypes encompassed by the claims other than a homozygous mouse exhibiting decreased time spent in a central region during an open field test, decreased time to fall during a rotorod test, decrease in time to fall off the accelerating rotorod and increased dose of metrazol to reach seizure the second stage of seizure .The specification discloses using the claimed mice for screening for agents that affect the phenotype of the claimed mice. However, because the specification has not taught the phenotype of the heterozygous mice encompassed by the claims and because the phenotype is not predictable, one of skill in the art would not know what to screen the mice for. Therefore, in light of the lack of guidance in the specification as set forth above and in light of the unpredictability of phenotype as set forth by the art, the specification fails to teach how to make and use the mice broadly encompassed by the claims.

2) The claims now recite that the claimed mouse has a genome comprising a null FPR-RS4 allele wherein the null allele comprises exogenous DNA. The claims broadly encompass insertion of exogenous DNA anywhere within the FPR-RS4 gene. The specification teaches making an insertion disruption in the FPR-RS4 gene using homology-targeting arms comprising SEQ ID NO:3 and SEQ ID NO:4, which are regions within the FPR-RS4 gene. The specification does not teach where with respect to the structure of the protein product the insertion will occur or teach that that the resulting disruption is null. The specification does not teach any other placement of an insertional disruption or what placements will result in a null allele. The

specification defines a null allele as a disruption, wherein there is no significant expression of the FPR-RS4 gene, however, the specification does not define the limits of "significant expression". Furthermore, the specification has contemplated a null allele (page 4, lines 15-16) but has not demonstrated that the described gene disruption (page 53, lines 19-24) results in a null FPR-RS4 allele.

3) Claim 43 encompass a transgenic mouse whose genome comprises exogenous DNA in SEQ ID NO:1. However, SEQ ID NO:1 is a cDNA that does not occur naturally in the genomic DNA of a mouse. The specification teaches only how to insert an exogenous DNA into the endogenous genomic FPR-RS4 sequence that differs from SEQ ID NO:1 in that in contains non-coding intronic DNA interspersed through the exonic DNA sequence set forth by SEQ ID NO:1. The skilled artisan would not know how to insert an exogenous DNA into a genomic sequence that does not exist. Therefore, the specification fails to enable making the mouse of claim 43.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above, the breadth of the claims with respect to the phenotype of the claimed mice, and the unpredictability of phenotype of transgenic animals, it would have required undue experimentation for one skilled in the art to make and use the claimed invention with a reasonable expectation of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1) Claims 6,8,9,40,41,43-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mansour (*Development*, 1993, vol. 117, pp 13-28) in view of Gao (1998, Genomics, Vol. 51, pages 270-276).

Mansour taught transforming a mouse ES cell with a nucleic acid construct targeting the int-2 gene, resulting in an inactivating insertion of a selective marker gene into the endogenous int-2 locus (page 14, col. 1, paragraph 3), and using said cell to generate a mouse whose genome comprises a disruption in the int-2 gene (for specific method steps see page 15, col. 2, paragraph 3). The targeting construct comprised both a neo resistance gene and a visible lacZ marker (page 14, col. 1, paragraph 3). Mansour differs from the claimed invention in that the targeting construct does not disrupt the FPR-RS4 gene.

However, at the time the claimed invention was made, Gao taught the cloning of the mouse FPR-RS4 gene (entire document and for further sequence detail GenBank Accession No. AF071182).

Accordingly, it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to make cells and a knockout mouse having a disruption in a targeted gene as taught by Mansour wherein the gene was FPR-RS4 as taught by Gao. One of ordinary skill in the art would have been sufficiently motivated to replace the int-2 gene with the FPR-RS4 gene, as it was an art-recognized goal to determine the physiological role of a gene of interest by the generation of a knockout mouse. One of ordinary skill in the art would have been sufficiently motivated to disrupt the FPR-RS4 gene to determine its role in relation to other FPR genes, as described by Gao (1998, Genomics, Vol. 51, pages 270-276).

Note that absent any phenotypic requirements for the claimed transgenic mouse, the combination of the cited prior art is sufficient to make obvious the claimed invention. Mansour discloses the applicability of gene targeting to many other genes so that a correlation can be drawn between the malfunctioning gene and the manifestation of disease (page 41, column 2, 2nd full paragraph). The skilled artisan could expect to obtain the claimed mouse with a reasonable level of success because it was routine in the art to knock out genes and because the claims are so broad as to encompass any phenotype, any mouse obtained by the method would fulfill the limitations of the claims.

Thus, the claimed invention is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Valarie Bertoglio
Examiner
Art Unit 1632

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